

### ***Remarks***

#### ***Support for the Amendments***

Support for the amendments to claims 1, 2, 13, 16, 23, 30 and 71 can be found throughout the specification. Specifically, support for the amendments to claims 1, 2 and 23 can be found in claims 12 and 29 as originally filed, and in the specification at page 12, lines 16-20; and at page 24, line 29 through page 26, line 24. The amendments to claims 13, 16 and 30 are sought to update the dependency of these claims upon the cancellation of claims 12 and 29. The amendment to claim 71 is sought to correct a minor and inadvertent typographical error. Hence, these amendments do not add new matter and their entry and consideration are respectfully requested.

#### ***Status of the Claims***

By the foregoing amendments, claims 1, 2, 13, 16, 23, 30 and 71 are sought to be amended, and claims 12 and 29 have been cancelled without prejudice or disclaimer. Upon entry of the foregoing amendments, claims 1, 2, 5-11, 13-28, 30-33, 66, and 69-72 are pending in the application, with claims 1, 2, 23 and 66 being the independent claims.

#### ***Summary of the Office Action***

In the Office Action dated November 26, 2003, the Examiner has made three rejections of, and one objection to, the claims. Applicants respectfully request that the Examiner reconsider all outstanding rejections and objections and that they be withdrawn.

Applicants respectfully submit that the Examiner has improperly issued this Office Action as a final Office Action. In the Office Action at page 2, the Examiner indicates that

all of the current rejections have been made on new grounds. Furthermore, Loeb *et al.* was not previously cited to Applicants, and the rejections raised in light of this reference are on new grounds. In addition, the Examiner has not indicated that any of the new grounds of rejection raised for the first time in the present Office Action were necessitated by Applicants' amendment of the claims. Finally, the Examiner has not made any other indications as to why such rejections should be made final. Accordingly, Applicants respectfully assert that the final rejection made in the present Office Action is improper. *See* MPEP § 706.07. Applicants therefore respectfully request that the finality of this Office Action be withdrawn.

***The Rejection Under 35 U.S.C. § 102(e) Over Loeb***

In the Office Action at pages 2-3, the Examiner has rejected claims 1-2, 5-6, 16-18, 20, 33 and 66 under 35 U.S.C. § 102(e), as being anticipated by Loeb, *et al.* (U.S. Patent No. 6,395,524, Document B cited on Form PTO-892 attached to paper No. 11132003; hereinafter "Loeb"). Applicants respectfully traverse this rejection.

Present claim 1 (and hence, claims 5-6, 16-18 and 20 that depend ultimately therefrom and that are also rejected) recites a method of identifying, analyzing or typing a polymorphic DNA fragment in a sample of DNA, comprising contacting the sample of DNA with one or more DNA polymerases, wherein the DNA polymerases are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a synthesized DNA molecule; amplifying the polymorphic DNA fragment within the sample; and analyzing the amplified polymorphic DNA fragment.

Present claim 2 recites a method of producing amplified copies of a polymorphic DNA fragment which comprise substantially no non-templated 3' terminal nucleotides, comprising contacting a DNA sample with one or more DNA polymerases, wherein the DNA polymerases are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a synthesized DNA molecule; and amplifying the polymorphic DNA fragment within the DNA sample.

Present claim 33 depends ultimately from claim 23. Claim 23 recites a kit comprising one or more DNA polymerases, wherein the DNA polymerases are mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a synthesized DNA molecule. Applicants note that the Examiner has rejected dependent claim 33, but not the broader, independent claim 23. Applicants believe that perhaps the Examiner meant to issue her rejection to the independent claim, claim 23, and have structured their argument as such.

Present claim 66 recites a method for amplifying a double stranded DNA molecule, comprising: (a) providing a first and second primer, wherein the first primer is complementary to a sequence at or near the 3'-terminus of the first strand of the DNA molecule and the second primer is complementary to a sequence at or near the 3'-terminus of the second strand of the DNA molecule; (b) hybridizing the first primer to the first strand and the second primer to the second strand in the presence of the one or more DNA polymerases which have been mutated to reduce, substantially reduce or eliminate the ability of the polymerases to add non-templated 3' nucleotides to a synthesized nucleic acid molecule under conditions such that a third DNA molecule complementary to the first strand

and a fourth DNA molecule complementary to the second strand are synthesized; (c) denaturing the first and third strands, and the second and fourth strands; and (d) repeating steps (a) to (c) one or more times.

The Examiner states that Loeb does not disclose a DNA polymerase which is "mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a DNA molecule." *See* Office Action, at page 2, section 2, third paragraph. However, the Examiner contends that this phrase is interpreted to mean that "the mutated polymerase increases the fidelity of synthesized DNA in a polymerase chain reaction," and hence that the disclosure of Loeb anticipates the instant claims. *See* Office Action, at page 2 last paragraph through top of page 3. Applicants respectfully disagree with these contentions.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*; 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). This burden is not met by Loeb.

In order to anticipate the claims of the present invention under *Kalman* and *PPG Industries*, Loeb would necessarily have to disclose a polymerase that is mutated to at least be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a synthesized DNA molecule, as such a polymerase is recited in each of the

independent claims of the present invention. Applicants submit, and the Examiner has acknowledged, that Loeb does not disclose such a polymerase. Instead, Loeb discloses a method of identifying mutated polymerases that have altered (*e.g.* increased) fidelity. Nowhere in Loeb is there a disclosure of a mutated polymerase that is at least substantially reduced the ability to add one or more non-templated nucleotides to the 3' terminus of a synthesized DNA molecule.

Loeb defines fidelity as "intended to refer to the accuracy of template-directed incorporation of complementary bases in a synthesized DNA strand relative to the template strand." *See* Loeb, at column 5, lines 47-50. The present specification defines "non-templated 3' terminal nucleotide addition" as:

[T]he propensity of an enzyme such as a DNA polymerase to incorporate one or more additional nucleotides, which are not found in the template strand at the 3' terminus of a newly synthesized nucleic acid molecule in a synthesis or amplification reaction, such as PCR. As a result of non-templated 3' nucleotide addition, the synthesized or amplification products (*i.e.* the newly synthesized DNA strand) will be longer by one or more nucleotides than is the template, in such a fashion that if the template is "n" nucleotides in length, the synthesis or amplification products will be "n+1," "n+2," "n+3," etc., nucleotides in length.

Specification, at page 24, line 29 through page 25, line 9. The polymerases disclosed in Loeb more accurately incorporate complementary bases in a synthesized DNA molecule relative to the template DNA molecule. In other words, as the ordinary artisan would readily understand, the fidelity increases described in Loeb relate to reduced misincorporation of bases *within* a template region. In contrast, the present invention relates to polymerases that are at least substantially reduced in their ability to add non-templated nucleotides to the 3' terminus of a synthesized nucleic acid molecule. As the ordinary artisan would readily

understand, the reduced propensity to add nucleotide(s) beyond the 3' terminus of a template molecule (as recited in the present claims), is fundamentally different from the reduced misincorporation of bases *within* a template region (as described in Loeb). Hence, the Examiner's contention that Loeb discloses the presently claimed methods, or polymerases having the characteristics recited in the presently claimed methods, is incorrect. That a polymerase may operate with "increased fidelity" does not *a priori* mean that the polymerase will exhibit reduced ability to add non-templated nucleotide(s) to the 3' terminus of a synthesized nucleic acid molecule.

In view of the foregoing remarks, Applicants submit that Loeb does not disclose every element of the presently claimed invention. Hence, in view of *Kalman*, Loeb cannot, and does not, anticipate the presently claimed invention. Reconsideration and withdrawal of the rejection of claims 1-2, 5-6, 16-18, 20, 33 and 66 under 35 U.S.C. § 102(e) over Loeb are respectfully requested.

***The Rejection Under 35 U.S.C. § 103(a) Over Loeb in view of Caetano-Anolles***

In the Office Action at pages 3-4, the Examiner has rejected claims 9-15 and 23-32 under 35 U.S.C. § 103(a) as being unpatentable over Loeb as applied to claims 1, 2, 5-6, 16-18, 20, 33 and 66 in view of Caetano-Anolles, *et al.* (WO 95/33853, Document N cited on Form PTO-892 attached to paper No. 11132003; hereinafter "Caetano-Anolles"). Applicants respectfully traverse this rejection. However, solely to expedite prosecution, and not in acquiescence to this rejection, claims 12 and 29 have been canceled. Thus, the portion of this rejection that may have applied to these claims has been rendered moot. Applicants

also respectfully traverse this rejection as it may apply to claims 9-11, 13-15, 23-28 and 30-32.

Present claims 9-11 and 13-15 depend ultimately from claim 1. Present claims 24-28 and 30-32 depend ultimately from claim 23. As discussed above, both independent claims 1 and 23 recite the use of DNA polymerases which have been mutated to at least substantially reduce their ability to add one or more non-templated nucleotides to the 3' terminus of a synthesized DNA molecule.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). In the present case, this burden has not been met.

The Examiner admits that Loeb does not disclose a mutated polymerase that is reduced in 3'-5' or 5'-3' exonuclease activity. The Examiner relies on the disclosure of Cateano-Anolles to cure this deficiency, and contends that it would have been obvious to one of ordinary skill in the art to modify the method of Loeb by applying the DNA polymerase of Caetano-Anolles. Applicants respectfully disagree with these contentions.

In addition to not disclosing a mutated polymerase that is reduced in 3'-5' or 5'-3' exonuclease activity, as noted above, Loeb also does not disclose a polymerase which is at

least substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a synthesized DNA molecule. This serious deficiency is not cured by the disclosure of Caetano-Anolles, and therefore the Examiner has not met the required burden.

By the Examiner's own acknowledgment (*see* previous Office Action (Paper No.10) at page 3, section 7, third paragraph), Caetano-Anolles provides no objective teaching that would have led one of ordinary skill to make and use a DNA polymerase mutated to at least substantially reduce the ability of the polymerase to add one or more non-templated nucleotides to the 3' terminus of a synthesized DNA molecule. Therefore, Caetano-Anolles does not cure the serious deficiencies in Loeb. Furthermore, there is no disclosure in Loeb or Caetano-Anolles that would have motivated one of ordinary skill in the art to have combined their disclosures in an attempt to make and use the presently claimed invention. Absent such suggestion and motivation, these references may not properly be combined. (*See Fine*, 5 USPQ2d at 1598.)

Applicants therefore submit that the Examiner has not met the required burden to establish a *prima facie* case of obviousness. Accordingly, it is respectfully requested that the rejection of claims 9-11, 13-15, 23-28 and 30-32 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

***The Rejection Under 35 U.S.C. § 103(a) Over Loeb in view of Huo***

In the Office Action at pages 4-5, the Examiner has rejected claims 21 and 22 under 35 U.S.C. § 103(a) as being unpatentable over Loeb as applied to claims 1, 2, 5-6, 16-18, 20, 33 and 66 in view of Huo (U.S. Patent No. 5,922,535, Document A cited on Form PTO-892



attached to paper No. 11132003; hereinafter "Huo"). Applicants respectfully traverse this rejection.

Present claim 21 (and hence, claim 22 that depends ultimately therefrom and that is also rejected) depends ultimately from claim 1. Present claim 1 recites the use of a DNA polymerase mutated to be substantially reduced in the ability to add one or more non-templated nucleotides to the 3' terminus of a synthesized DNA molecule. For reasons discussed above, which are reiterated and incorporated herein by reference, Loeb is seriously deficient as a primary reference. Huo does not cure this deficiency, as this reference also does not disclose, suggest or otherwise contemplate the use of such a mutated DNA polymerase. Hence, there is no disclosure or suggestion in Loeb or Huo that would have motivated one of ordinary skill in the art to have combined their disclosures in an attempt to make and use the presently claimed invention. Absent such suggestion and motivation, these references may not be properly combined. (*See Fine*, 5 USPQ2d at 1598.)

Applicants therefore submit that the Examiner has not met the required burden to establish a *prima facie* case of obviousness. Accordingly, it is respectfully requested that the rejection of claims 21 and 22 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

***Provisionally Allowable Subject Matter***

In the Office Action at page 5, the Examiner has objected to claims 7-8, 19 and 69-72 as being dependent upon a rejected base claim. In making this objection, the Examiner also notes that these claims would be allowable if rewritten in independent form including all of the limitations of the rejected base claim. Applicants acknowledge this identification of

provisionally allowable subject matter. However, Applicants respectfully traverse this objection, and submit that in view of the foregoing remarks, all of the currently pending claims are allowable. Reconsideration and withdrawal of the objection to these claims are therefore respectfully requested.

***Conclusion***

All of the stated grounds of rejection and objection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and objections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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